

Claims

What is claimed is:

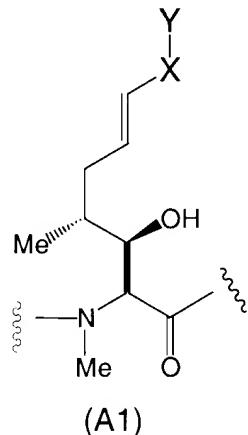
1. A cyclosporin analog of formula I or a pro-drug or a pharmaceutically acceptable salt thereof:

A---B---Sar-MeLeu-Val-MeLeu-Ala---U---MeLeu-MeLeu-MeVal
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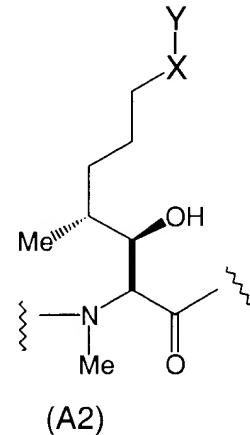
(I)

wherein

10 (i) A is of the formula:



or



wherein:

15 X is absent, -C1-C6 alkyl-, or -C3-C6 cycloalkyl-;

Y is selected from the group consisting of:
aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

(ii) B is - α Abu-, -Val-, -Thr- or -Nva-; and

20 (iii) U is -(D)Ala-, -(D)Ser-, -[O-(2-hydroxyethyl)(D)Ser]-, -[O-(acyl)(D)Ser]- or -[O-(2-acyloxyethyl)(D)Ser]-.

25 2. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, wherein in formula I, B is - α Abu-, and U is -(D)Ala-.

3. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, wherein in formula I:

(i) A is of the formula A1 or A2, wherein:

X is absent; and

5 Y is selected from the group consisting of:

aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

(ii) B is - α Abu-; and

(iii) U is -(D)Ala-.

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4. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

Compound of formula (I), where A=A1, X is absent and Y = (2'-Me)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-F)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-CF₃)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (2'-Br)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (2'-Cl)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (2'-OMe)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (3'-Cl)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-Cl)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (3'-Br)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-Br)Ph; B is - α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (3'-COOCH₃)Ph; B is - α Abu-; and U is -(D)Ala-;

35 Compound of formula (I), where A=A1, X is absent and Y = (4'-COOCH₃)Ph; B is - α Abu-; and U is -(D)Ala-;

\Compound of formula (I), where A=A1, X is absent and Y = (2'- Naphthalene);
B is α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-t-butyl)Ph; B is α Abu-; and U is -(D)Ala-;

5 Compound of formula (I), where A=A1, X is absent and Y = (pentafluoro)Ph; B is α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (4'-AcO-)Ph; B is α Abu-; and U is -(D)Ala-;

10 Compound of formula (I), where A=A1, X is absent and Y = (4'-OCH₃)Ph; B is α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (3', 4'-OMe₂)Ph; B is α Abu-; and U is -(D)Ala-;

15 Compound of formula (I), where A=A1, X is absent and Y = (2',5'-Me₂)Ph; B is α Abu-; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = Pyridine; B is α Abu; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = Pyrrole; B is α Abu; and U is -(D)Ala-;

20 Compound of formula (I), where A=A1, X is absent and Y = (N-methyl) Pyrrole; B is α Abu; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = Thiophene; B is α Abu; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = Oxazole; B is α Abu; and U is -(D)Ala-;

25 Compound of formula (I), where A=A2, X is absent and Y = (2'-Me)Ph; B is α Abu; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (S)Ph; B is α Abu; and U is -(D)Ala-;

Compound of formula (I), where A=A1, X is absent and Y = (SO)Ph; B is α Abu; and U is -(D)Ala-; and

30 Compound of formula (I), where A=A1, X is absent and Y = (SO₂)Ph; B is α Abu; and U is -(D)Ala-.

5. A chemical process for preparing a cyclosporin analog of formula I as claimed in Claim 1, comprising reacting a compound of formula I, wherein A= -MeBmt-, with:

5 a. an olefin of formula $\text{CH}_2=\text{CH-X-Y}$, wherein X and Y are as defined in Claim 1, and

 b. a catalyst;

 in the presence of a lithium salt in an organic solvent and optionally converting the product of said reaction into a pharmaceutically acceptable salt.

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6. The process of claim 5, wherein the catalyst is Grubb's ruthenium alkylidene, Grubbs dihydroimidazole ruthenium catalyst, Schrock-Hoveyda molybdenum catalyst, Nolan's catalyst, a benzylidene catalyst or a molybdenum catalyst.

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7. A chemical process for preparing a cyclosporin analog of formula I as claimed in Claim 1, comprising:

20 a. reacting a compound of formula I, wherein A= -MeBmt- with:

 i. an olefin of formula $\text{CH}_2=\text{CH-X-Y}$, wherein X and Y are as defined in Claim 1; and

 ii. a catalyst;

 in the presence of a lithium salt in an organic solvent; and

 b. hydrogenating the product of step a in an organic solvent under hydrogen with a catalyst;

 and optionally converting the product of said reaction into a pharmaceutically acceptable salt.

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8. The chemical process as claimed in Claim 7, wherein the catalyst in step (a) (ii) is Grubb's ruthenium alkylidene, Grubbs dihydroimidazole ruthenium catalyst, Schrock-Hoveyda molybdenum catalyst, Nolan's catalyst, a benzylidene catalyst or a molybdenum catalyst.

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9. The chemical process as claimed in Claim 7, wherein step (b) is performed at room temperature.

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10. The chemical process as claimed in Claim 9, wherein the catalyst in step (b) is Palladium on carbon or Platinum Oxide.

11. A pharmaceutical composition, said composition comprising at least one cyclosporin analog of formula I as claimed in Claim 1, said cyclosporin analog being present alone or in combination with a pharmaceutically acceptable carrier or excipient.

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12. A method for treating autoimmune diseases in a subject, which comprises the step of administering to said subject a therapeutically effective amount of at least one cyclosporin analog of formula I as claimed in Claim 1.

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13. The method of Claim 12, wherein said autoimmune disease is selected from conical cornea, keratitis, dysophia epithelialis cornea, leukoma, Mooren's ulcer, scleritis and Grave's ophthalmopathy.

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14. A method for preventing organ transplantation rejection in a subject, which comprises the step of administering to said subject a therapeutically effective amount of at least one cyclosporin analog of formula I as claimed in Claim 1.